

# Cognition and Neuroimaging in Depression

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National Institute of Mental Health



# Disclosure

- Funding
  - Intramural research program/NIMH
  - No funding from industry
- Listed on a patent application submitted for the use of ketamine and its metabolites in depression. I have assigned my right on the patent to the US government

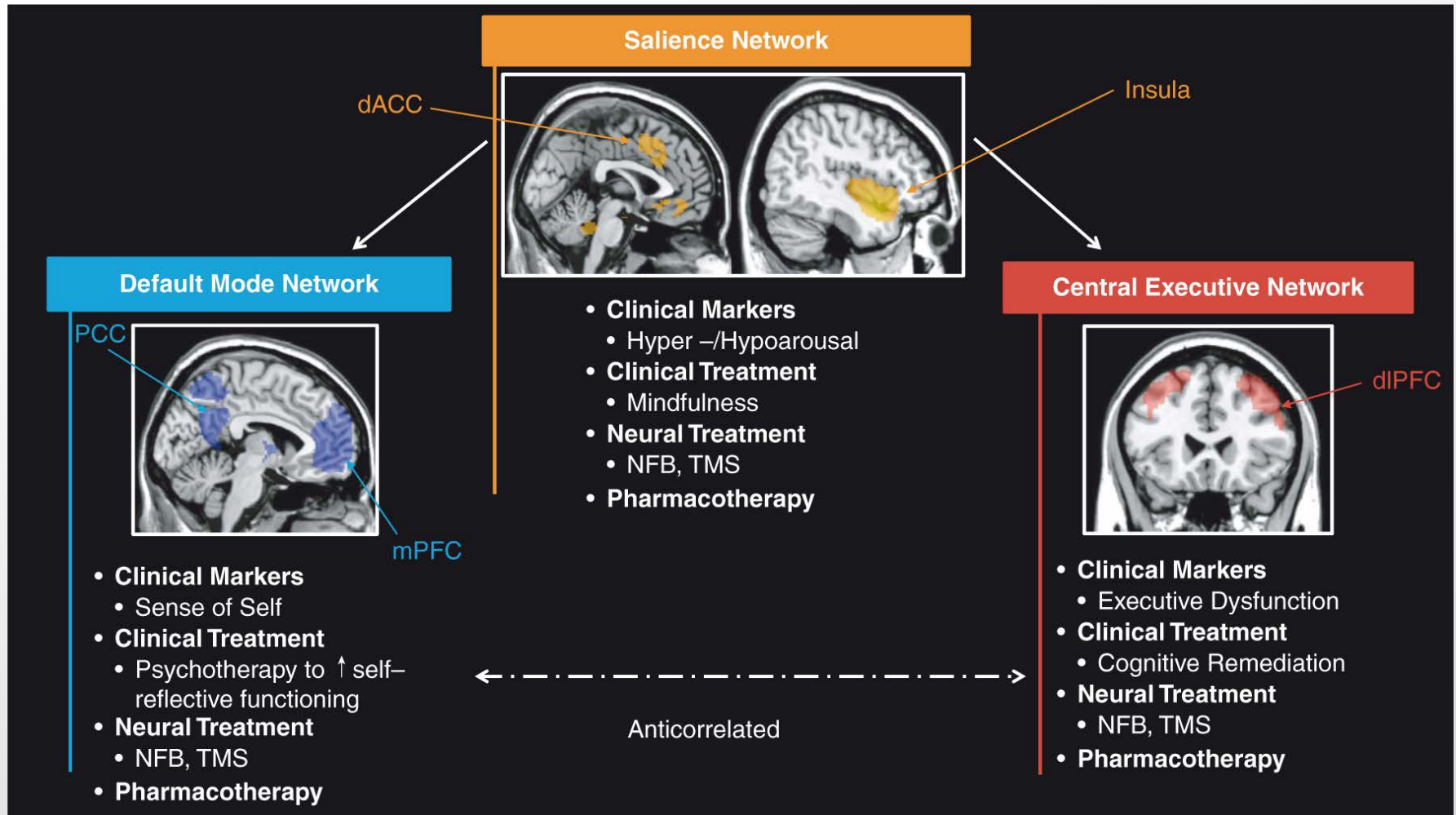


National Institute  
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# Cognition and Neuroimaging in Depression

- The triple network model: potentially a unified framework of cognitive dysfunction in depression
- Aberrant cognitive domains in depression
- Using the resting state, and undirected cognition, to interrogate dysfunctional processing in depression

# The Triple Network Model



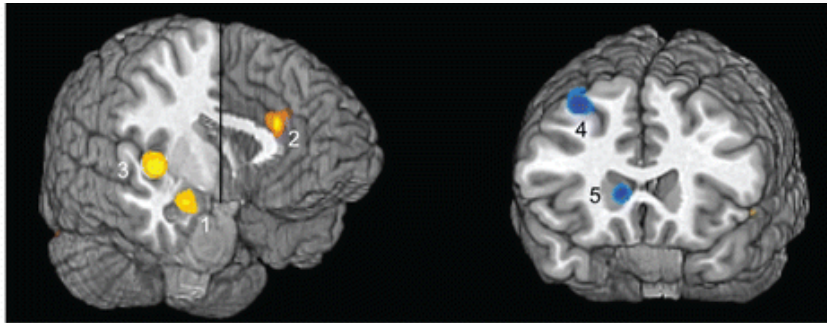
# MDD and Cognitive Domains

- Affective Processing
  - Bias towards negative stimuli in depression
- Attention
  - Dot probe tasks
- Working memory and Executive function
  - N-back tasks, delayed matching tasks
- Reward Processing
  - Gambling tasks, monetary incentive tasks

# MDD and Cognitive Domains

- **Affective Processing**
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# Affective Processing in Depression



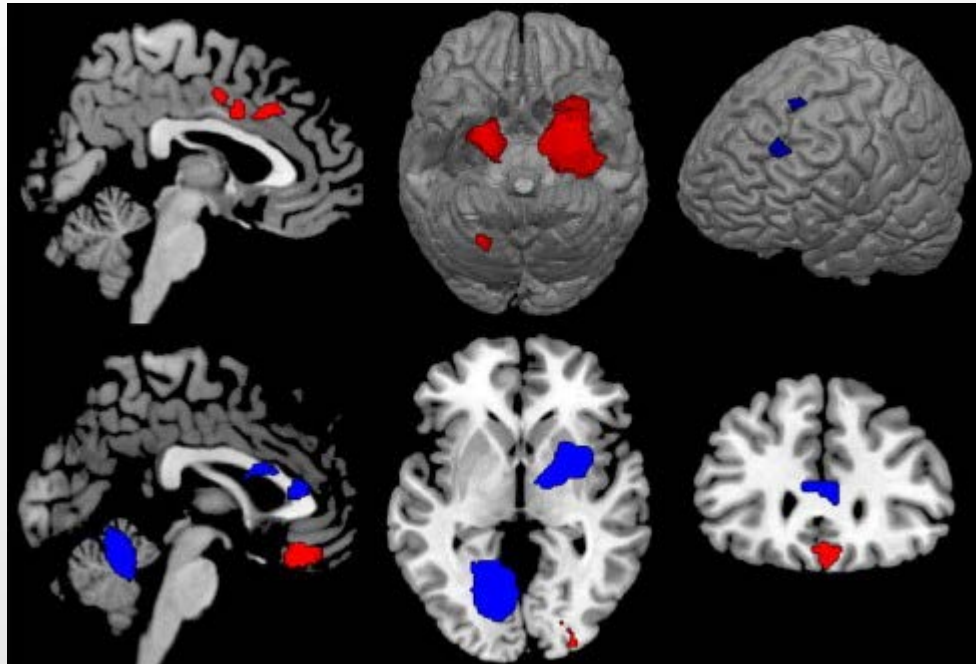
| Structure                          | Direction of Effect    | Valence Specific Effect? | Talairach Coordinates | Cluster Size (mm <sup>3</sup> ) | Number |
|------------------------------------|------------------------|--------------------------|-----------------------|---------------------------------|--------|
| Amygdala                           | Depressed > Comparison | Yes                      | 24, -4, -13           | 318                             | 1      |
| Dorsal anterior cingulate cortex   | Depressed > Comparison | Yes                      | -2, 30, 20            | 196                             | 2      |
| Insula and superior temporal gyrus | Depressed > Comparison | Yes                      | -38, -6, -8           | 834                             | 3      |
| Precentral gyrus                   | Depressed > Comparison | Yes                      | -30, -15, 44          | 621                             | -      |
| Middle temporal gyrus              | Depressed > Comparison | Yes                      | -39, -64, 17          | 440                             | -      |
| Dorsolateral prefrontal cortex     | Comparison > Depressed | Yes                      | 30, 13, 47            | 1,380                           | 4      |
| Dorsolateral prefrontal cortex     | Comparison > Depressed | No                       | -22, 27, 42           | 949                             | -      |
| Caudate body                       | Comparison > Depressed | No                       | 10, 20, 6             | 382                             | 5      |

- Meta-Analysis
- 14 rCBF and 24 fMRI studies
- Hyper-reactivity in the Salience network in response to negative vs. positive or neutral stimuli
- Hypo-reactivity in DLPFC (Executive network)
- Depressed subjects also showed reduced striatal response to positive stimuli

# Affective Processing in Depression

Negative Emotions

Positive Emotions



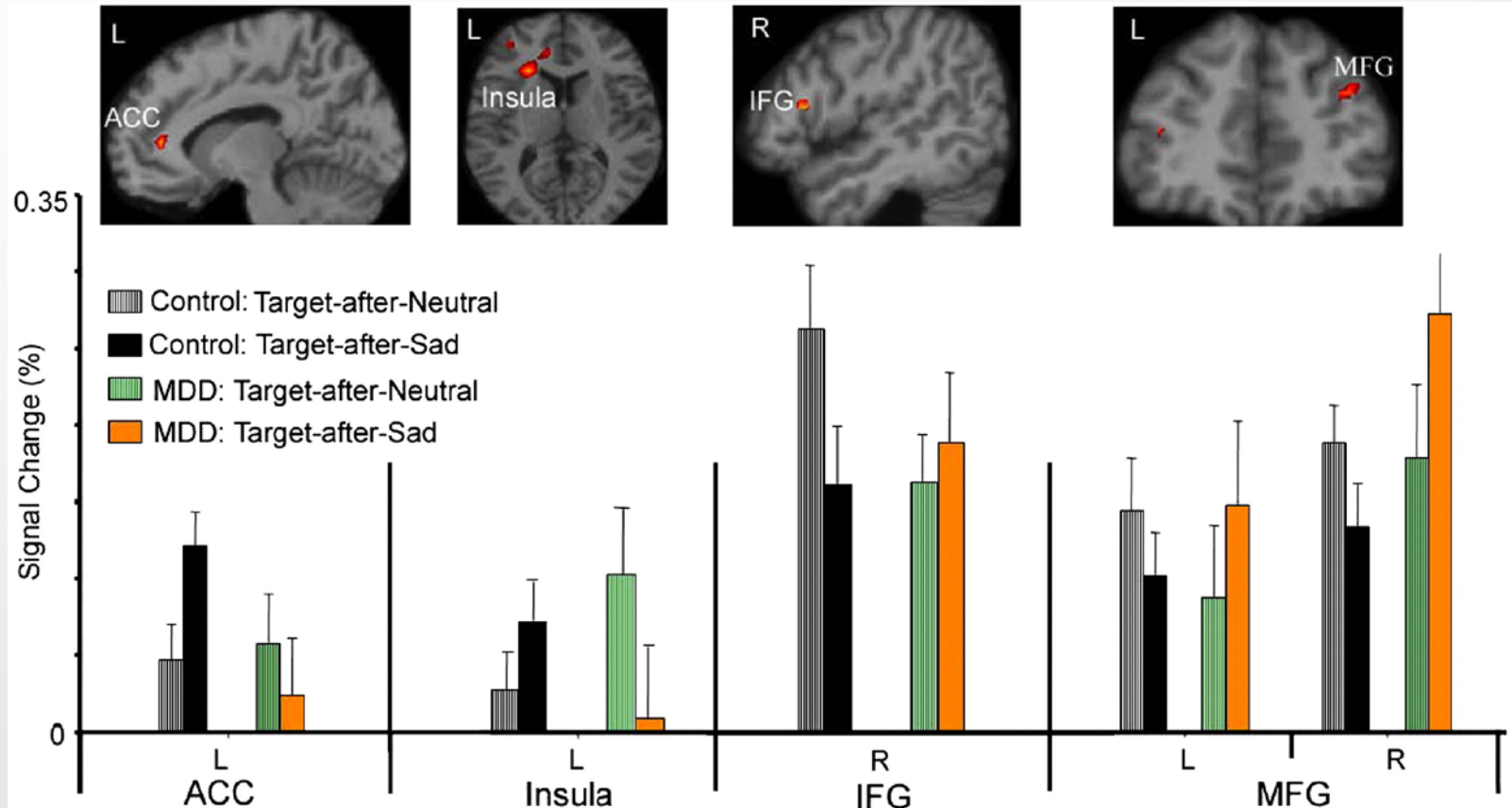
- Meta-analysis
- 44 fMRI studies
- Hyperactivation to negative stimuli and hypoactivation to positive stimuli



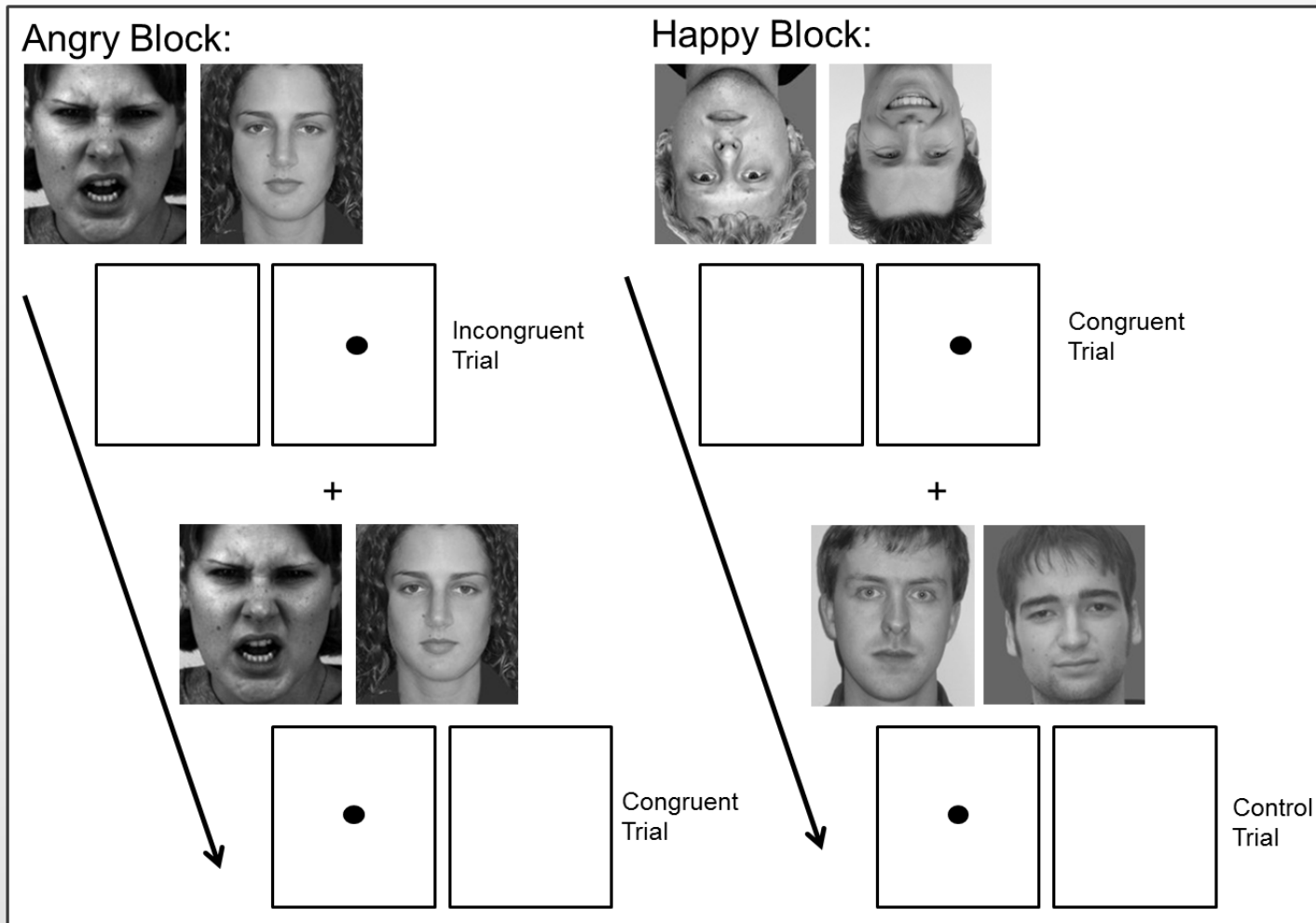
# MDD and Cognitive Domains

- Affective Processing
  - Bias towards negative stimuli in depression
- **Attention**
  - Dot probe tasks, distractor stimuli
- Working memory and Executive function
  - N-back tasks, delayed matching tasks
- Reward Processing
  - Gambling tasks, monetary incentive tasks

# Attention Processing in Depression



# Attention and Affective Processing – Dot Probe task



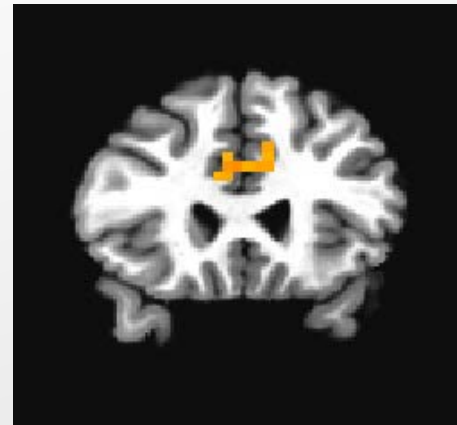
# Attention and Affective Processing – Dot Probe task

Main Effect of  
Emotion

Reward Areas



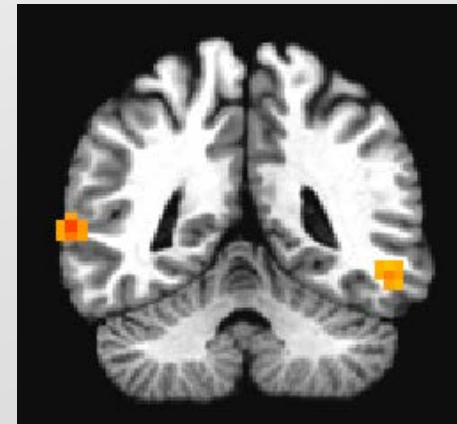
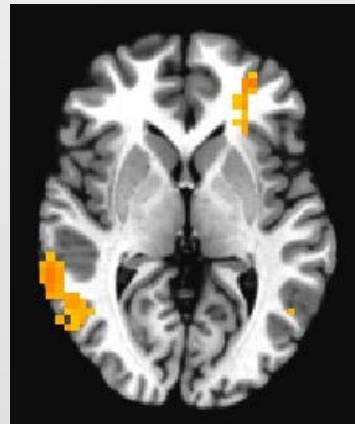
Salience Network Areas



Parahippocampal  
DMN Related



Emotion by  
Group Interaction



# MDD and Cognitive Domains

- Affective Processing
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- **Reward Processing**
  - Gambling tasks, monetary incentive tasks

# Reward Processing in Depression

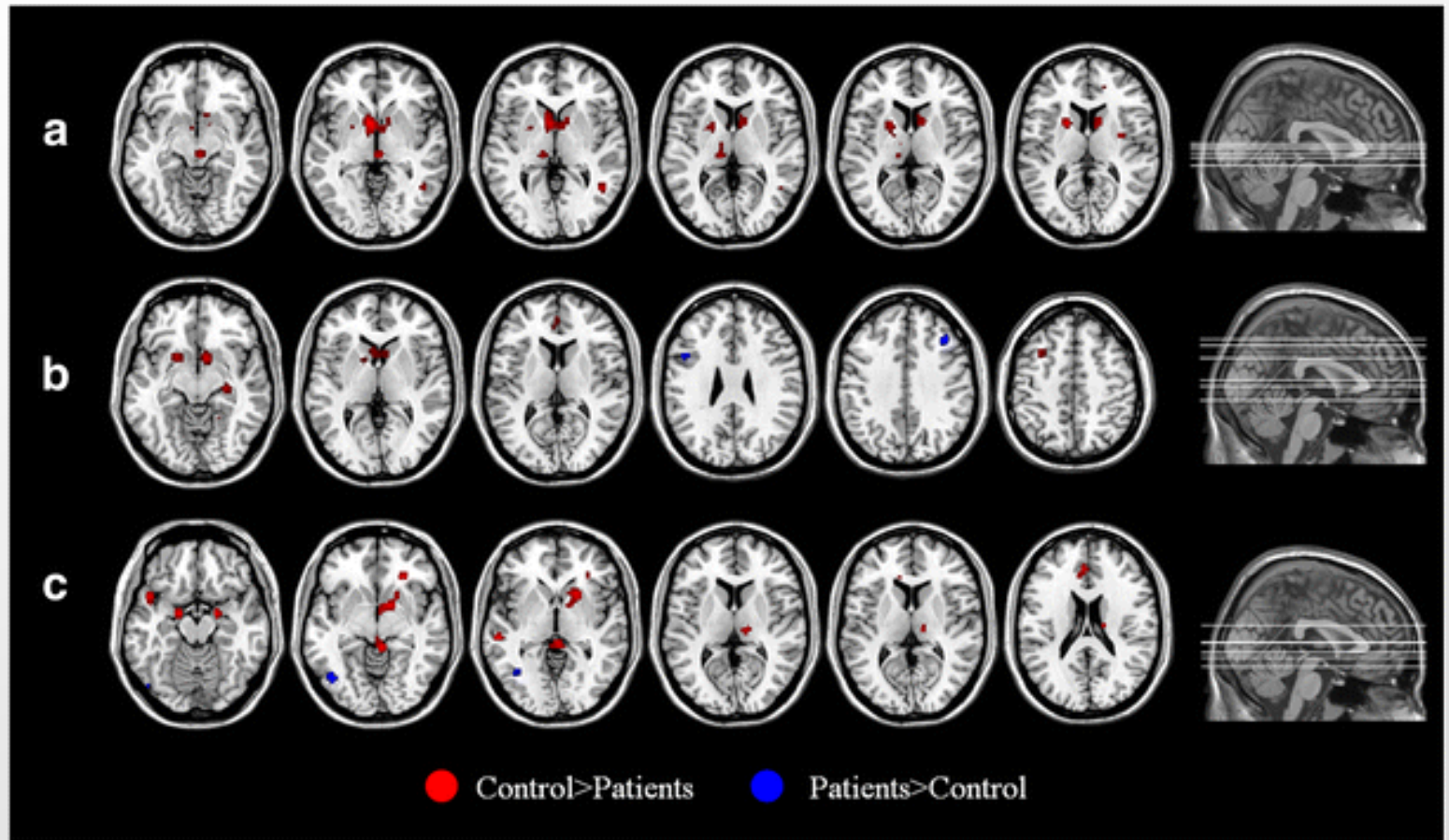
- Anhedonia is a cardinal symptom of depression
- Dysfunction associated with all aspects of reward processing, including reward anticipation, motivation, and consummatory pleasure.
- Evidence for abnormalities in mesocorticolimbic dopaminergic pathways
- “Wanting” or approach motivation associated with orbitofrontal cortex, anterior cingulate, and nucleus accumbens

# Reward Processing in Depression

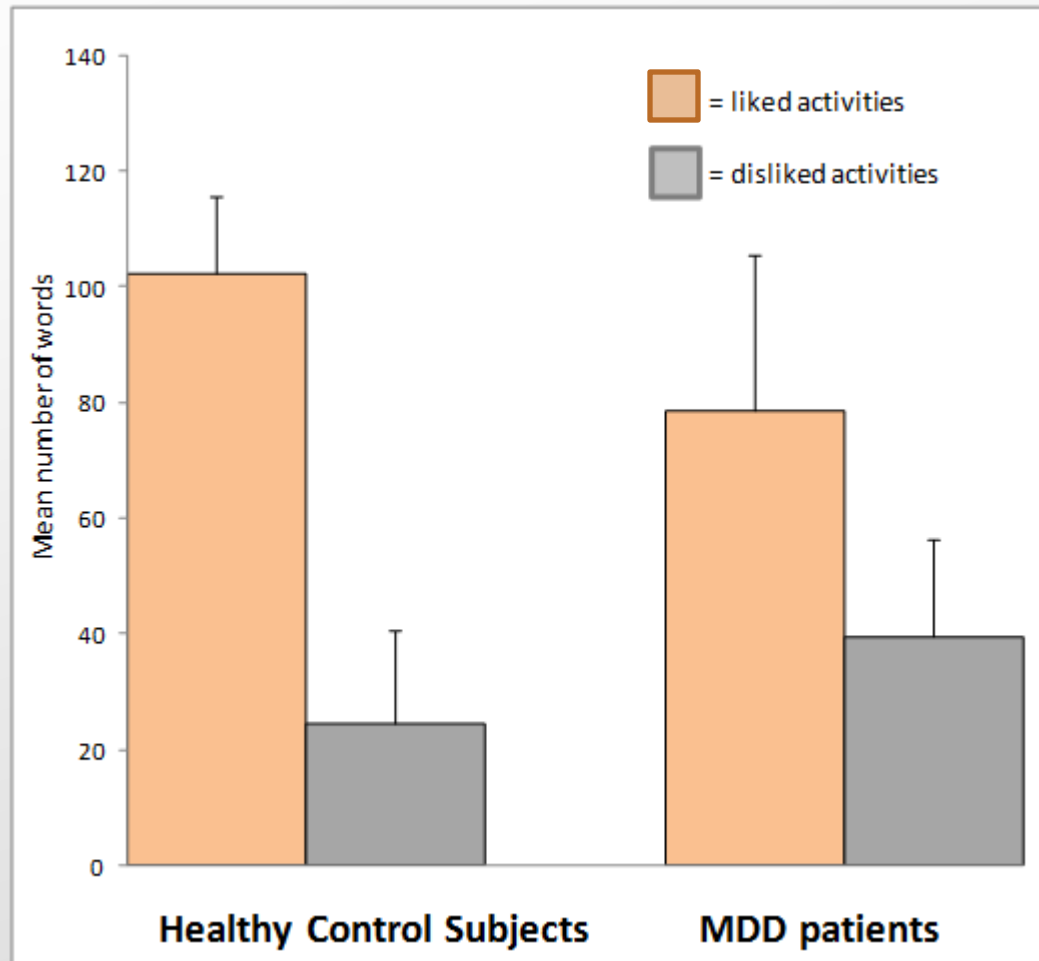
Consummatory  
Anhedonia

Anticipatory  
Anhedonia

Emotional  
Processing



# Reward Processing in Depression





# Reward Processing in Depression

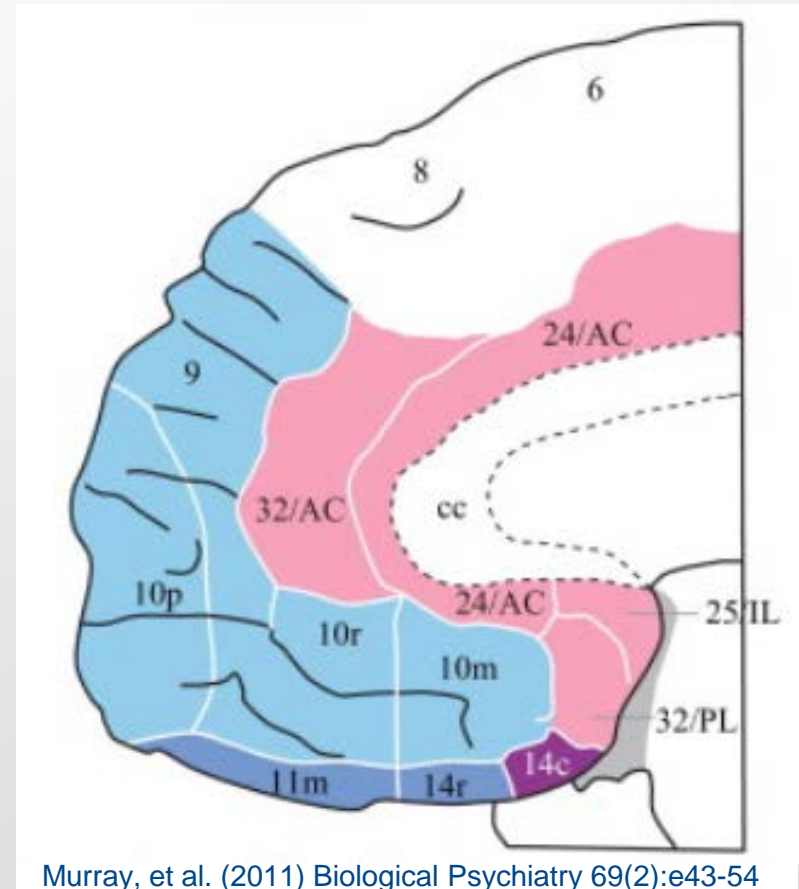
|  | <b>SNAITH-S</b> | <b>JAMS</b>    | <b>BAS-Total</b> | <b>BIS</b>    | <b>Chapman<br/>Total<br/>Anhedonia</b> | <b>BDI-II</b>  |
|--|-----------------|----------------|------------------|---------------|--|----------------|
| <b>ACTIVITY<br/>WORDS<br/>'LIKED'</b>    | <b>-.532***</b> | <b>.581***</b> | <b>.551***</b>   | <b>-0.26</b>  | <b>-.667***</b>                        | <b>-.496**</b> |
|  |                 |                |                  |               |  |                |
| <b>ACTIVITY<br/>WORDS<br/>'DISLIKED'</b> | <b>.487**</b>   | <b>-.476**</b> | <b>-.473**</b>   | <b>.401**</b> | <b>.532***</b>                         | <b>.506***</b> |
|  |                 |                |                  |               |  |                |

# Suicidality and Depression

- Suicidality is a complex behavior, but has been shown to correlate with levels of anhedonia
- Suicidality also involves impulsivity and mood lability
- Acute suicidality is not well studied and neural correlates are poorly understood

# Suicidality in Depression

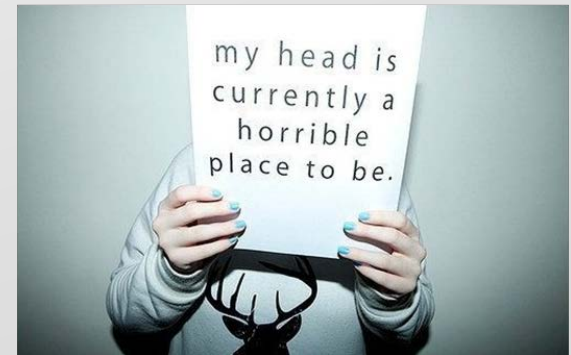
- Infralimbic cortex: Brodmann area 25, adjacent to subgenual cingulate
- Subjects with the highest suicidality scores showed the highest glucose metabolism in an anatomically defined ROI ( $R=0.593$ ,  $p=0.007$ )



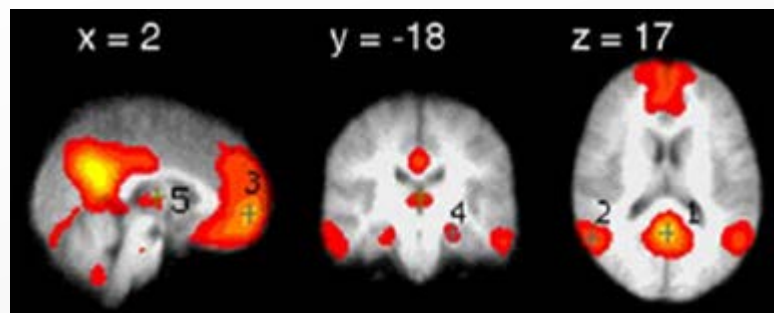
# Beyond Traditional Cognition: The Resting State in Depression



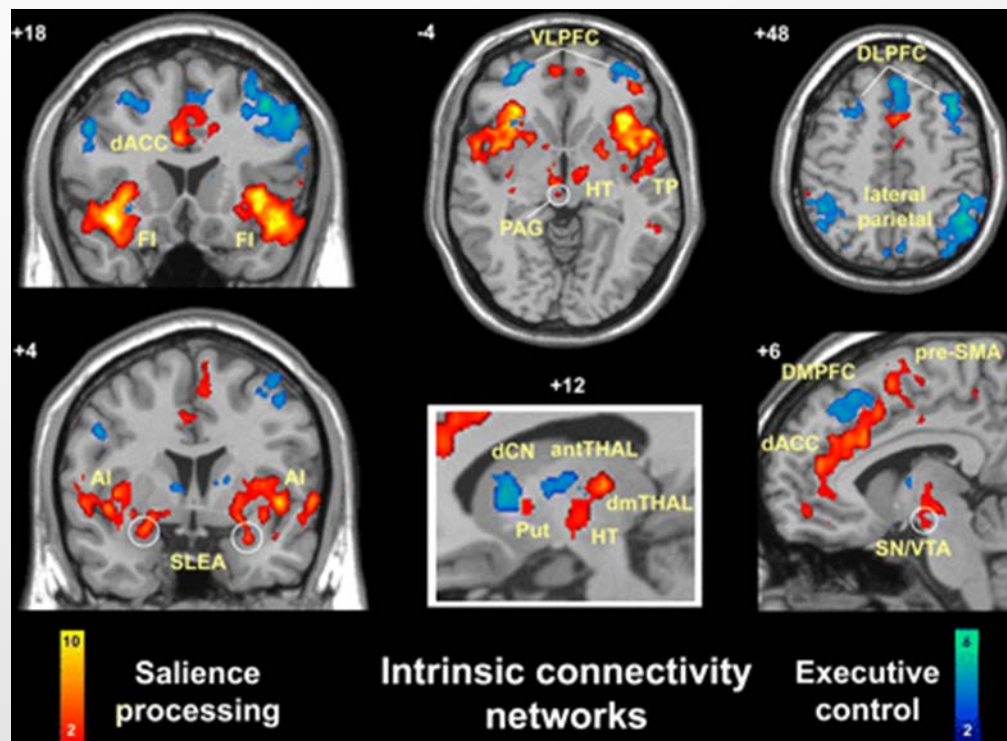
VS



# Intrinsic Cognitions: Triple Network Model

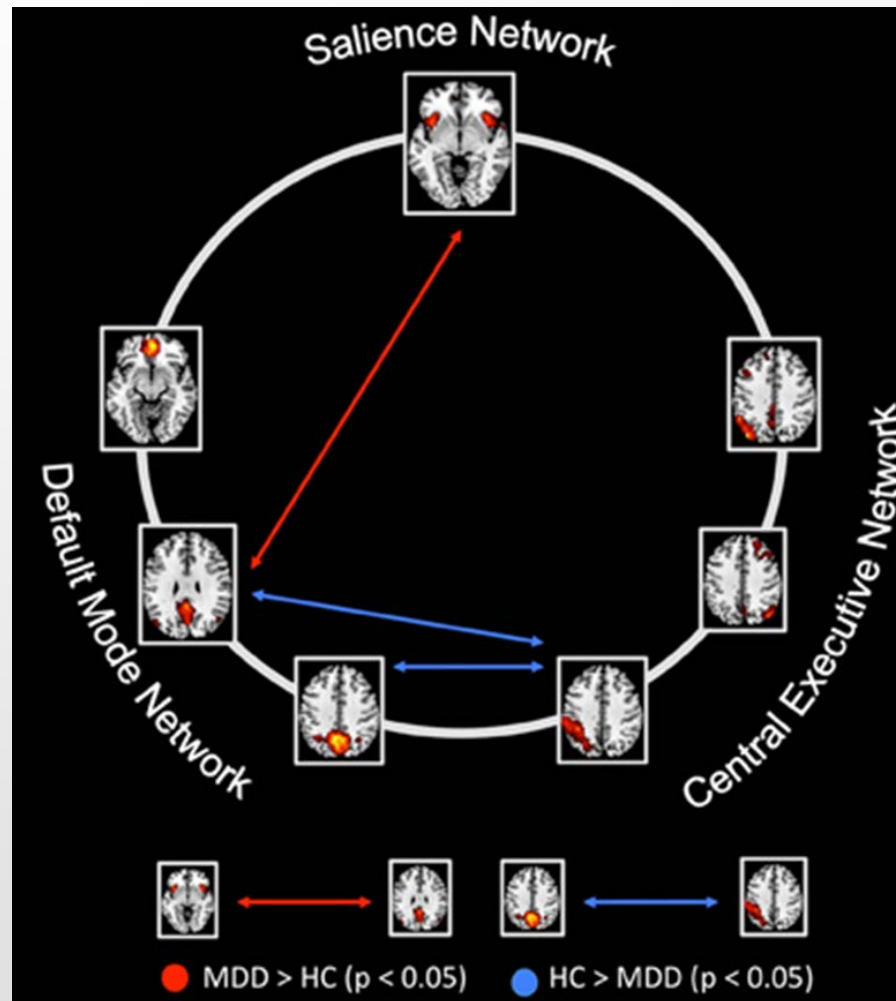


De Luca, et al. (2014) NeuroImage 29:1359-1367



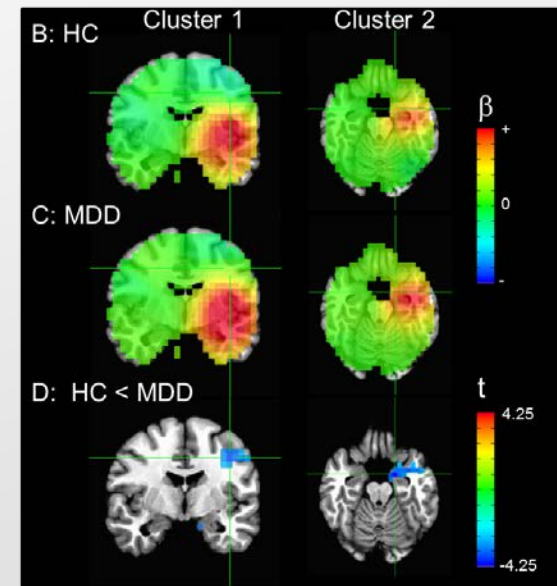
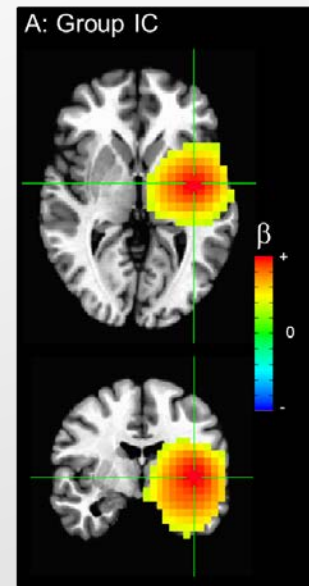
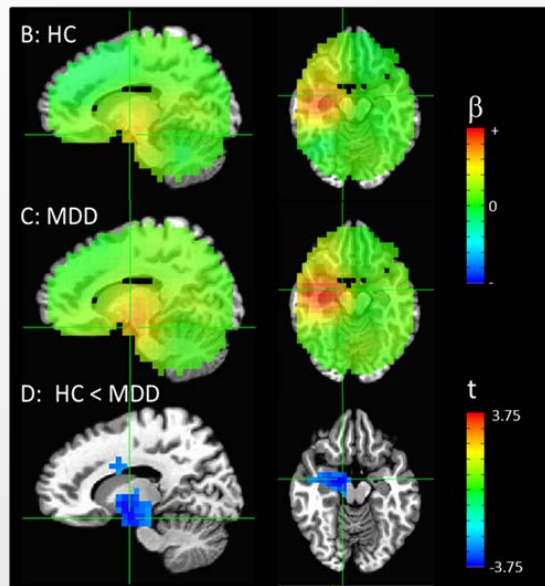
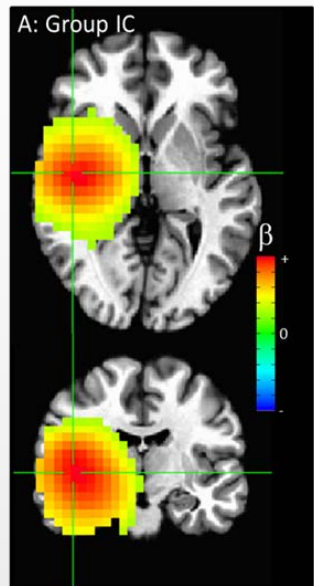
Seeley, et al. (2007) J Neurosci. 27(9):2349-2356

# Triple Network Model





# Depression and Salience

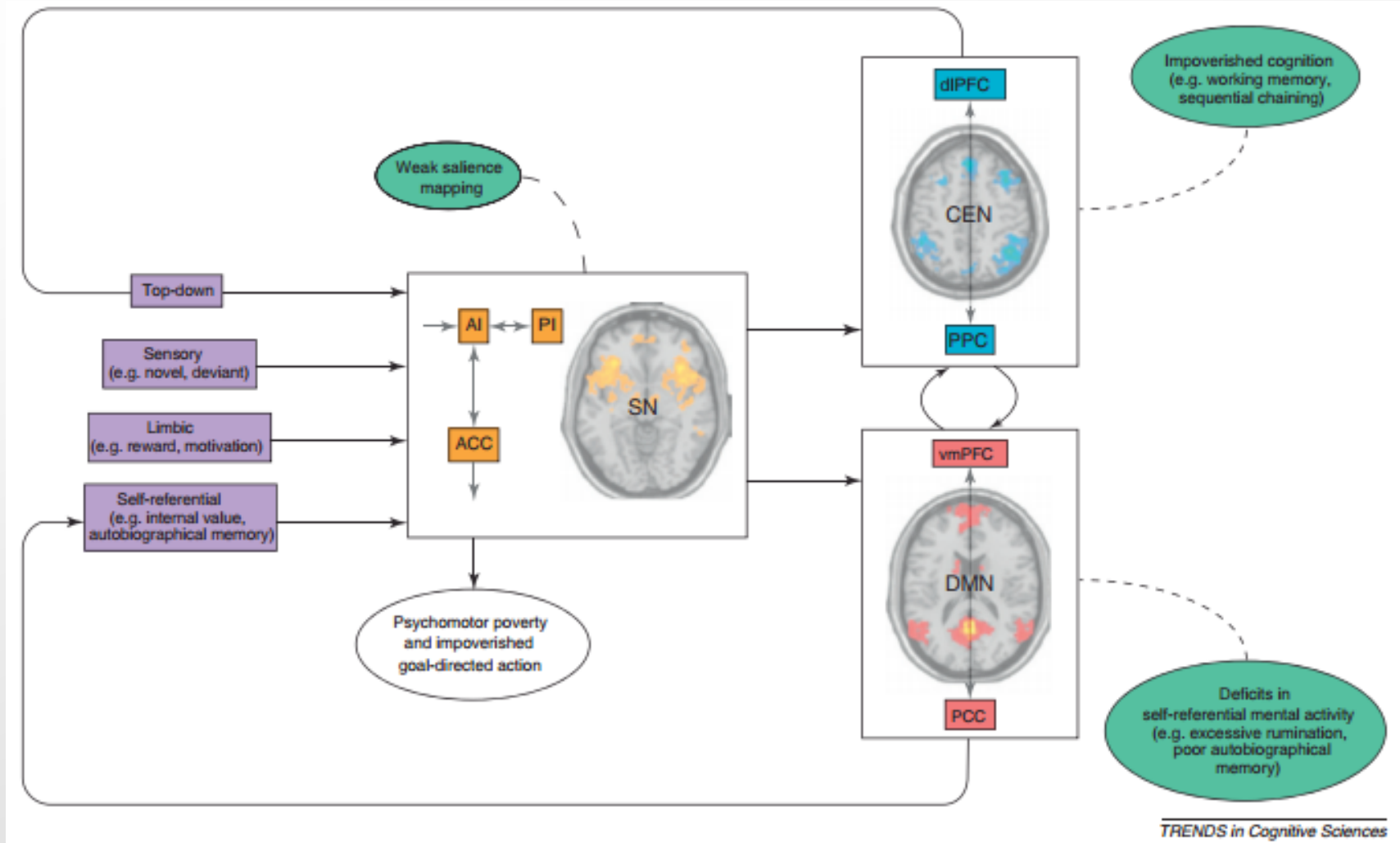


# Depression, Cognition, and Neuroimaging

- Alterations in Emotion Processing
  - Amygdala, Salience Network, Executive Network, Striatum
- Alterations in Attention
  - Salience and Executive Networks
- Alterations in Reward Processing
  - dACC (Salience Network), striatum
- Alterations in Executive Function
  - Executive Network
- Alterations in self directed cognition
  - Salience, Executive, and DMN, amygdala, and sgACC



# Depression, Cognition, and Neuroimaging



# Depression, Cognition, and Neuroimaging

- A triple-network model can be identified as a framework for cognitive function and psychiatric disorders
- Within this framework, we can test new drugs and therapies for their impact on each element and connection within this network
- Novel therapies or combinations of therapies can be utilized to normalize cognitive function in depression in a multifactorial way



# Assessing Cognitive Function

*Jenni Pacheco, Ph.D.*

February 3, 2016



National Institute  
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# Talk Overview

## Three Parts

- What is Cognition?
- How do we measure cognitive functioning?
- How do we determine cognitive improvement?

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- What is Cognition?
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# Overview of Cognitive Constructs

- Cognition is a multi-faceted concept, encompassing several constructs and processes. The sub-processes that fall under cognition are supported by higher-level brain functions and are crucial for interaction with the world.

- Attention
  - **Executive Function**
  - **Flexibility**
  - **Inhibition**
  - **Knowledge**
  - **Perception**
  - **Performance Monitoring**
  - Perception
  - Performance Monitoring
  - Planning
  - Reasoning
  - Working Memory
- Executive Function**
- 
- ```
graph LR; EF[Executive Function] --> Flex[Flexibility]; EF --> WM[Working Memory];
```

# Cognitive Dysfunction in Depression

Memory, attention and executive function are the cognitive domains that are most commonly identified as impaired in individuals with depression.

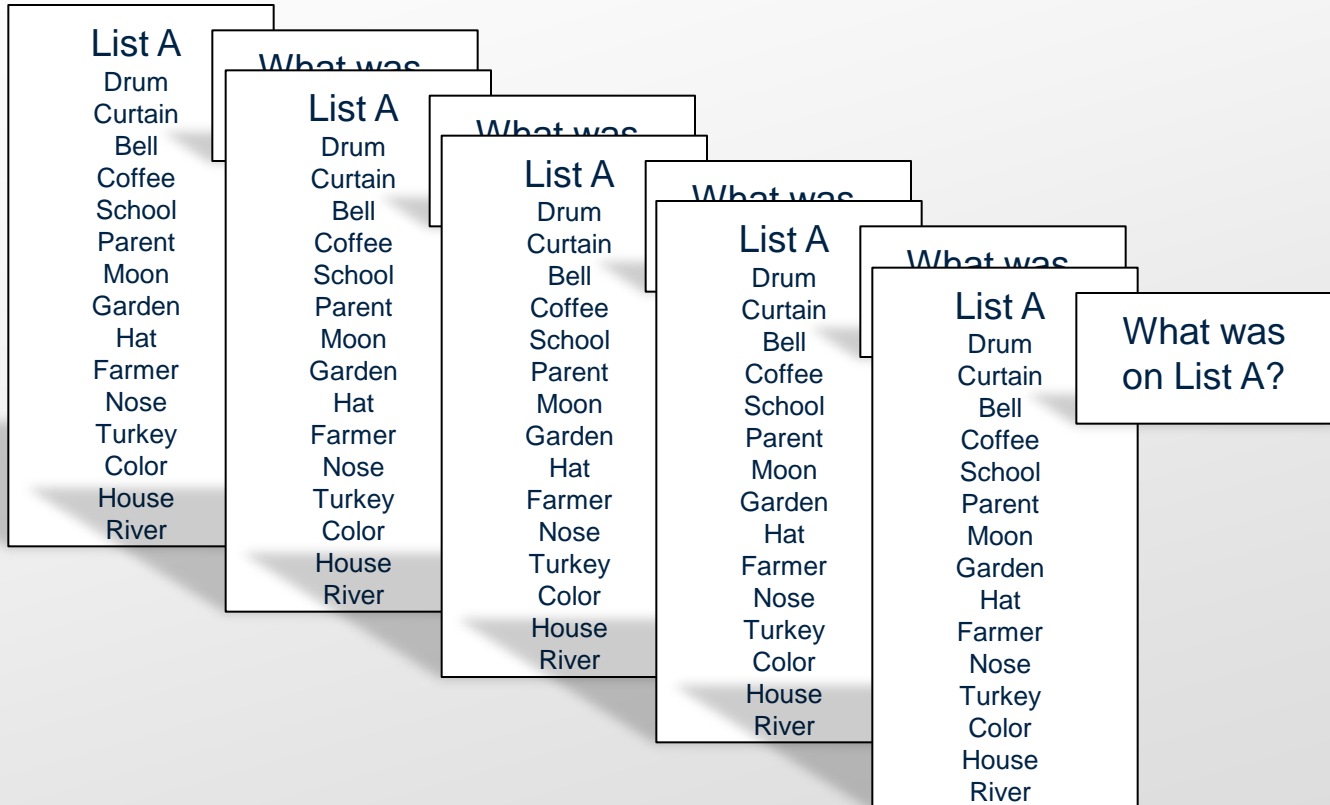
(Rock, 2014; Levin, 2007; Shenal, 2003)

## Memory

- Explicit memory, not implicit.
- In both recognition and recall tasks.
- Coordination between medial temporal lobe (hippocampus) and prefrontal cortex.
- Examples of tests:
  - Delayed match to sample
  - Paired associates learning
  - Pattern recognition memory
  - Story and list learning.

# Rey Auditory Verbal Learning Test

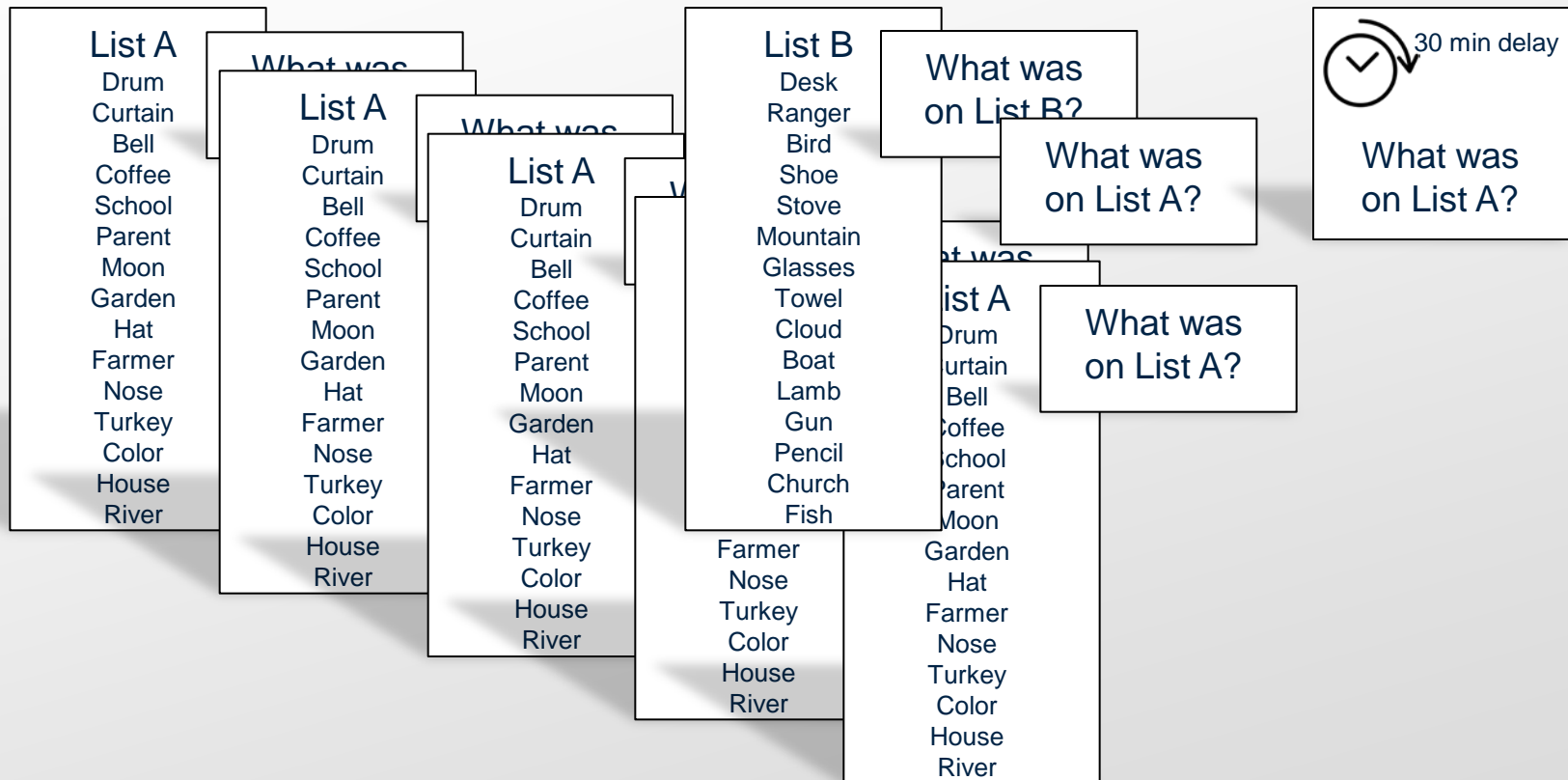
List learning with both an immediate and delayed component





# Rey Auditory Verbal Learning Test

List learning with both an immediate and delayed component



- Time to administer: Approximately 10 minutes of task and 30 minutes of delay.
- Provides measures of learning (number of words remembered from trial 1 to 5), susceptibility to interference from distractors, and delayed recall.

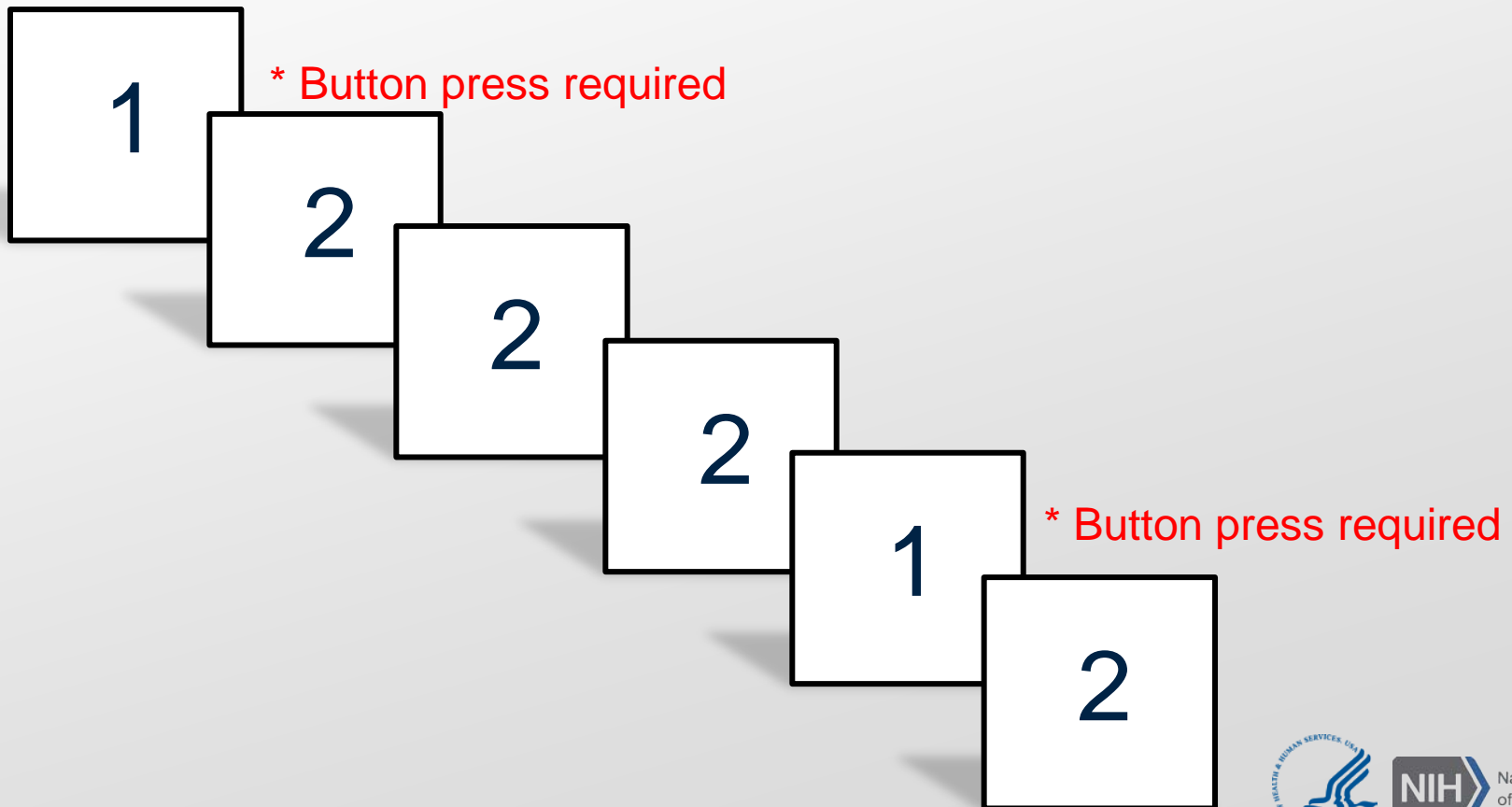
# Cognitive Dysfunction in Depression

## Attention

- Effortful attention, such as selective attention; not implicit processing
- Coordination between limbic system structures and the prefrontal cortex
- Examples of tests:
  - Choice reaction time tasks
  - Digit symbol coding
  - Sustained attention tasks
  - Continuous performance tasks

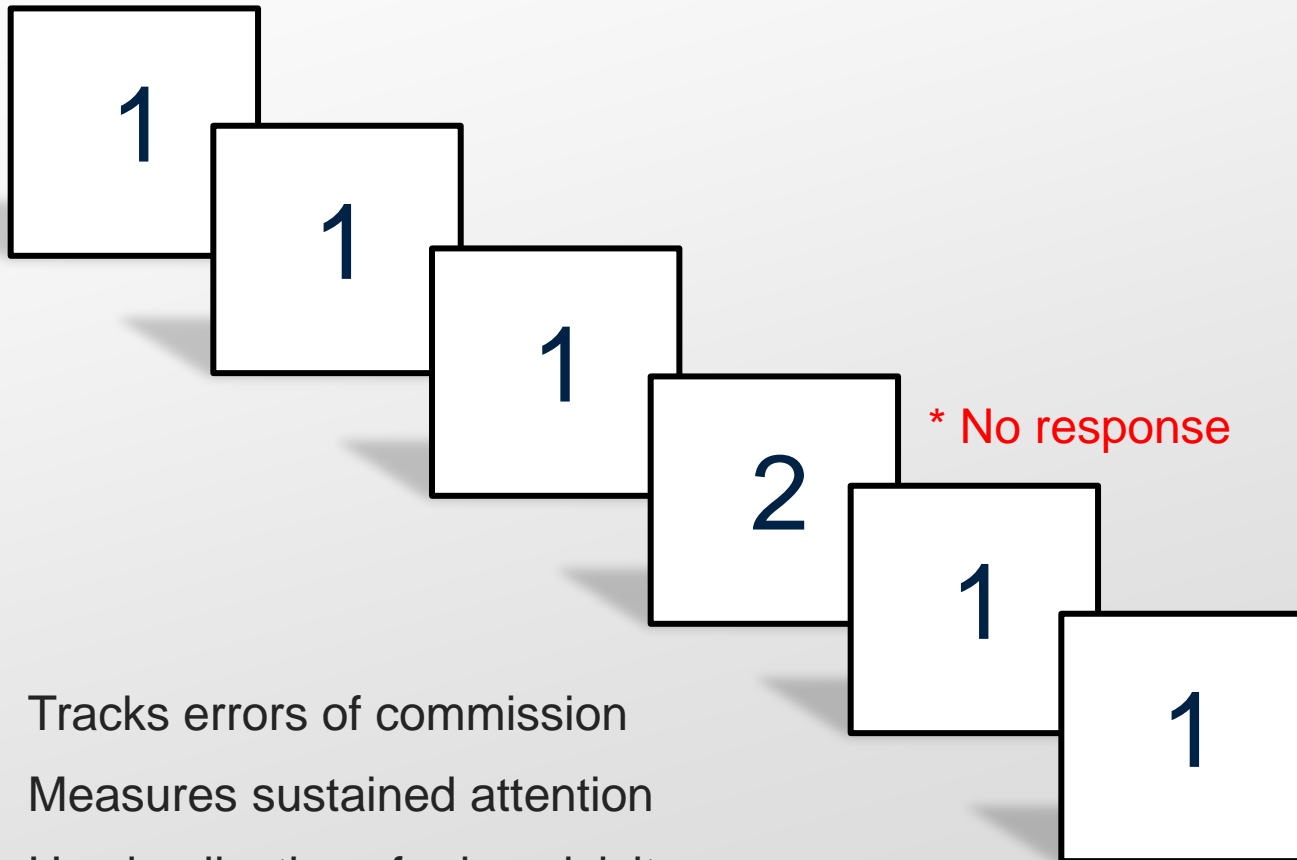
# Continuous Performance Task (CPT)

- CPT measures both sustained attention and selective attention.
- There are many different varieties of CPT, and each has a different administration time and trial set.



# Continuous Performance Task (CPT)

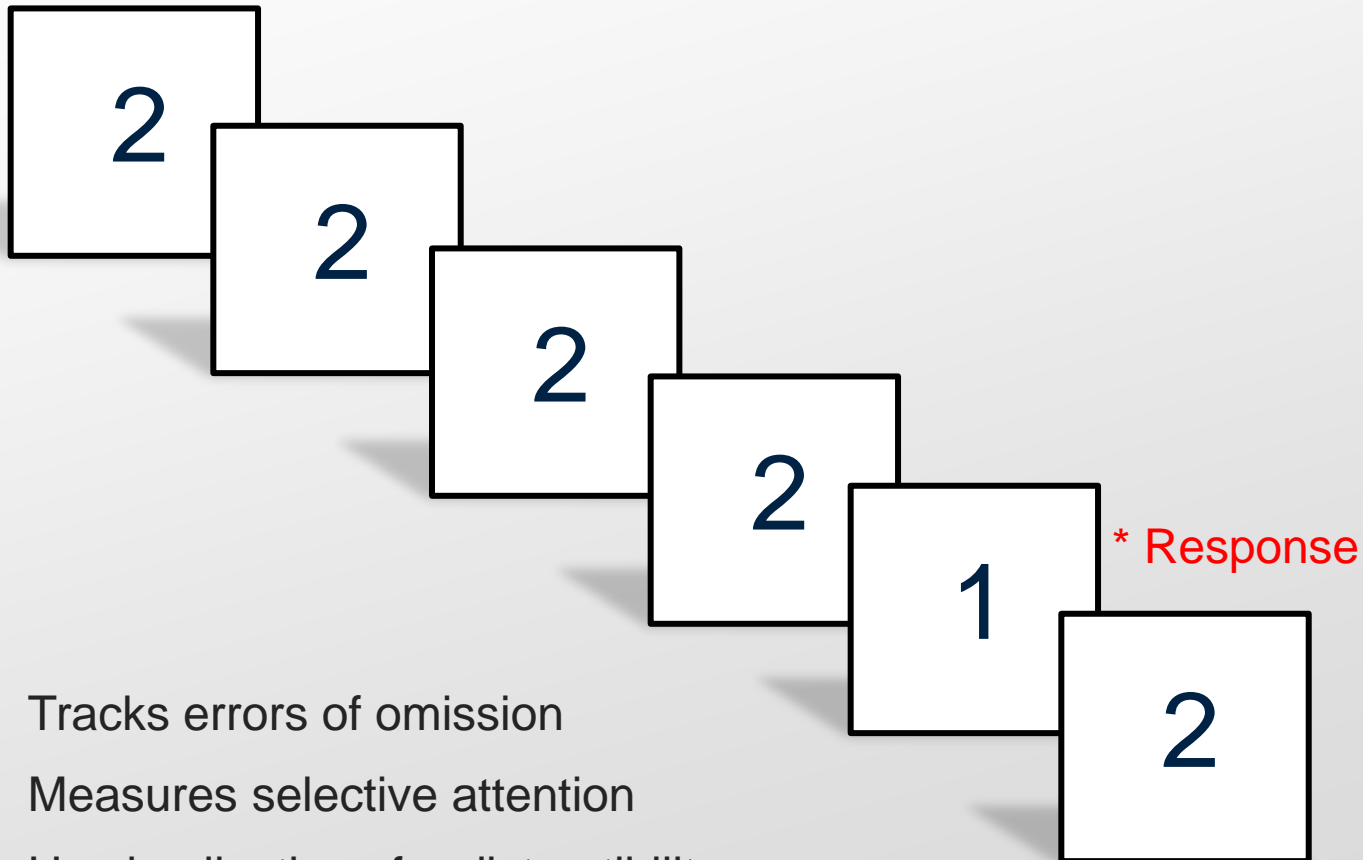
- High demand trial – maintain constant focus, be ready to “put the brakes on”



- Tracks errors of commission
- Measures sustained attention
- Has implications for impulsivity

# Continuous Performance Task (CPT)

- Low demand trial – focus on relevant stimuli, try not to “drift off”



- Tracks errors of omission
- Measures selective attention
- Has implications for distractibility

# Cognitive Dysfunction in Depression

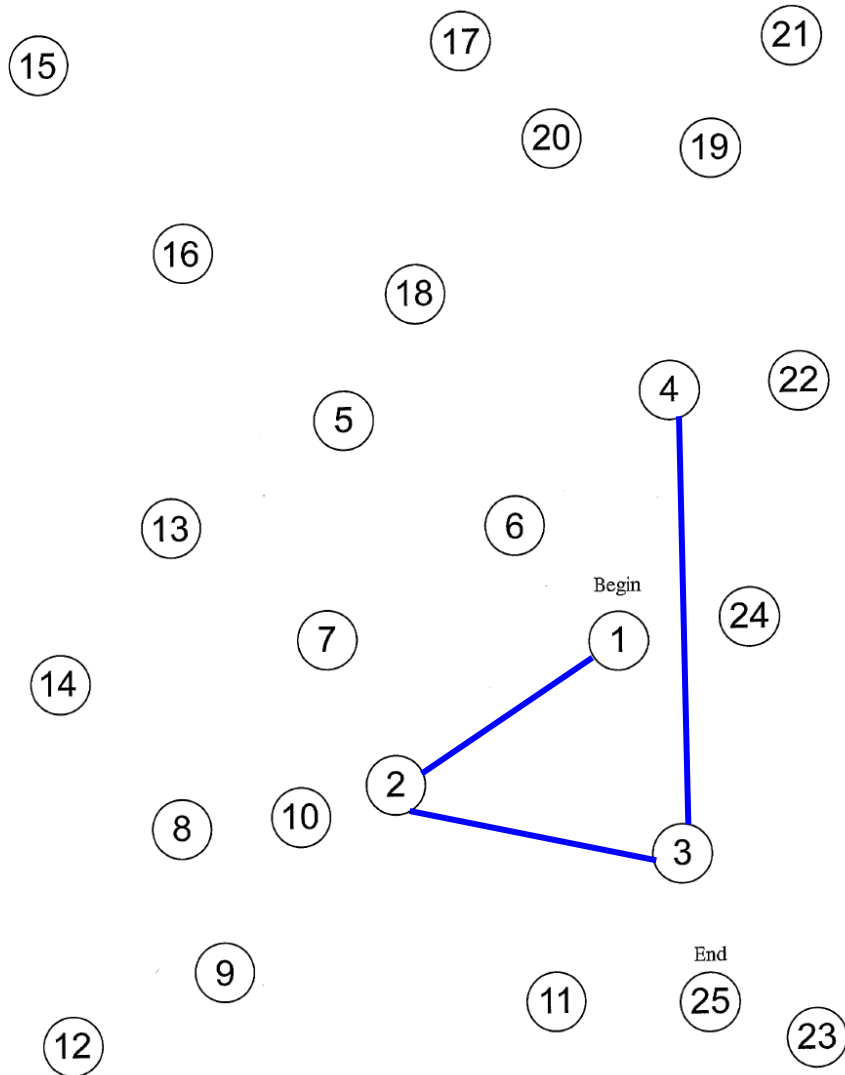
## Executive Function

- Encapsulates many higher-level cognitive functions, specifically planning, inhibition, problem solving, processing speed and set shifting.
- Coordination between the prefrontal cortex and several non-frontal structures to integrate information.
- Examples of tests:
  - Stroop
  - Wisconsin Card Sorting Test
  - Trail Making Test B
  - Tower of London
  - Spatial Span

# Trail Making Task A & B

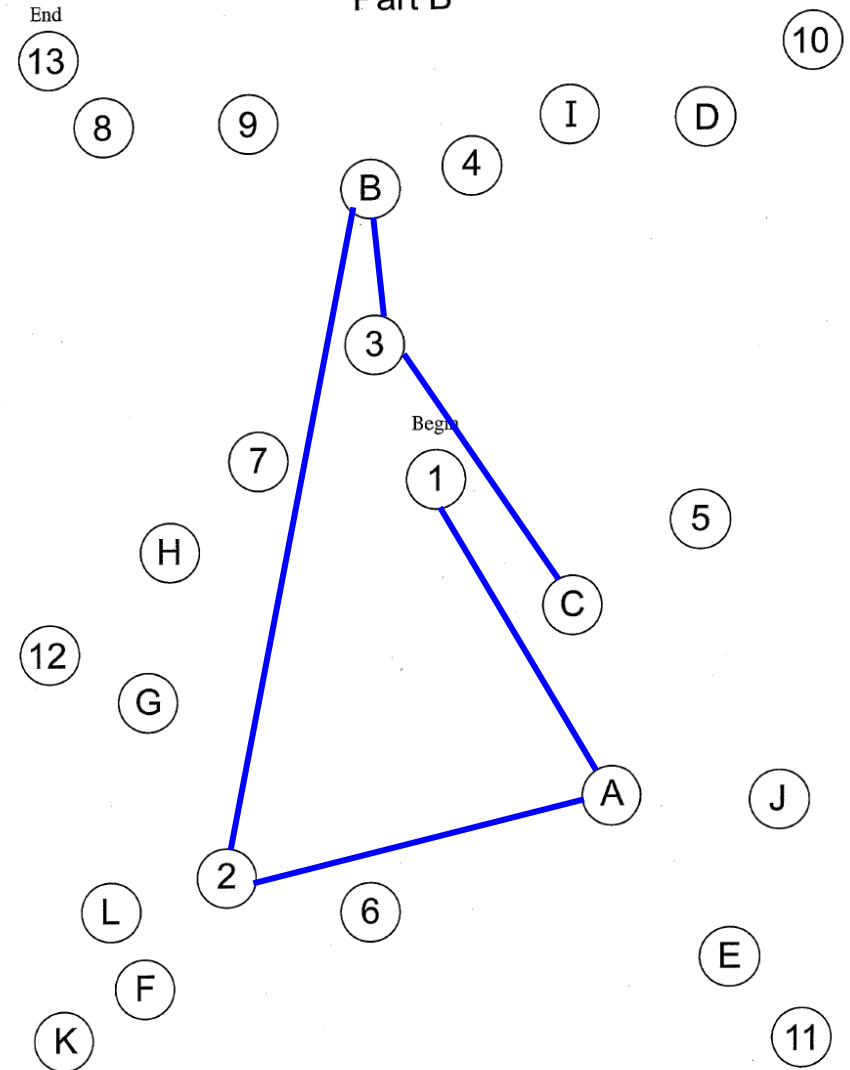
## TRAIL MAKING

### Part A



## TRAIL MAKING

### Part B



# Talk Overview

## Three Parts

- What is Cognition?
- How do we measure cognitive functioning?
- How do we determine cognitive improvement?



# Single Test vs. Battery of Tests

## A single test to assess cognition?

- A stand alone cognitive test has many benefits:
  - Easy and fast to administer
  - Less burden on participants and study staff
  - Simplicity of data analysis
- But is one test enough?
  - The entire multi-faceted and heterogeneous nature of cognition cannot be measured with one test
  - Task impurity: No single task is a pure measure of any construct (e.g., motivation + auditory perception + memory)
  - Individuals may score poorly for different reasons
  - Multiple measures provide converging validity: Every test has unique psychometrics (test-retest reliability, sensitivity), so if only one test is used to measure a cognitive domain, conclusions about the cognitive domain are conflated with the unique properties of that one test.

# MATRICS Consensus Cognitive Battery (MCCB)

- The **Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS)** initiative developed a standardized battery for use in clinical trials of cognition-enhancing interventions for schizophrenia research
- Test battery is founded on traditional neuropsychological tests
- Covers 7 cognitive domains
- Includes overlapping and converging measures for some domains
- Provides a score for each domain and an overall composite score
- Domains include:
  - Speed of Processing
  - Attention/Vigilance
  - Working Memory
  - Verbal Learning
  - Visual Learning
  - Reasoning and Problem Solving
  - Social Cognition

# MATRICS Test Battery (traditional neuropsych tests)

- No similar test battery standardization for depression, however the MATRICS battery has been used in clinical trials of pharmacological treatment of depression (Murrough, 2015), as well as studies of bipolar disorder (Burdick, 2011)
- Tests were selected for their psychometrics rather than specificity in terms of brain-related systems.
- A little “messy”; overlapping processes are required to perform the tests, resulting in significant part-to-whole correlations.
- Time to administer: between 60-90 minutes

# MATRICS Test Battery (traditional neuropsych tests)

| Cognitive Domain                     | Test                                          | Description                                                                                                                                                                                     |
|--------------------------------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Speed of Processing</b>           | Symbol Coding test                            | Timed paper-and-pencil test in which respondent uses a key to write digits that correspond to nonsense symbols                                                                                  |
|                                      | Category Fluency: Animal Naming               | Oral test in which respondent names as many animals as he/she can in 1 minute                                                                                                                   |
|                                      | Trail Making Test: Part A                     | Timed paper-and-pencil test in which respondent draws a line to connect consecutively numbered circles placed irregularly on a sheet of paper                                                   |
| <b>Attention/Vigilance</b>           | Continuous Performance Test – Identical Pairs | Computer-administered measure of sustained attention in which respondent presses a response button to consecutive matching numbers                                                              |
| <b>Working Memory</b>                | Spatial Span Test                             | Using a board on which 10 cubes are irregularly spaced, respondent taps cubes in same (or reverse) sequence as test administrator                                                               |
|                                      | Letter-Number Span                            | Orally administered test in which respondent mentally reorders strings of number and letters and repeats them to administrator                                                                  |
| <b>Verbal Learning</b>               | Hopkins Verbal Learning Test                  | Orally administered test in which a list of 12 words from three taxonomic categories is presented and the respondent is asked to recall as many as possible after each of three learning trials |
| <b>Visual Learning</b>               | Brief Visuospatial Memory Test                | A test that involves reproducing six geometric figures from memory                                                                                                                              |
| <b>Reasoning and Problem Solving</b> | Mazes Test                                    | Seven timed paper-and-pencil mazes of increasing difficulty that measure foresight and planning                                                                                                 |
| <b>Social Cognition</b>              | Managing Emotions test                        | Paper-and-pencil multiple-choice test that assesses how people manage their emotions                                                                                                            |

# CNTRACS Tests (circuit-based tests)

- The **Cognitive Neuroscience Test Reliability and Clinical Applications for Schizophrenia (CNTRACS)** consortium assembled a list of tasks that assess more narrow cognitive processes and demonstrate associations with activation in specific circuits and disruptions of those circuits in patients with schizophrenia.
- A subset of these tasks were selected for further development/optimization. Scores on these tests are only modestly intercorrelated (compared to the MATRICS battery), suggesting that they assess more discrete cognitive circuits and processes.

# CNTRACS Tests (circuit-based tests)

| Cognitive Domain                         | Test                                           | Description                                                                                                                                                                                                             |
|------------------------------------------|------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Goal Maintenance</b>                  | The AX-Continuous Performance Task             | Pairs of letter are presented and target pairs receive one response, and non-target pairs receive another. With a majority of the items being target pairs, this test measures goal maintenance and sustained attention |
|                                          | Dot Pattern Expectancy Task                    | A version of CPT using dot pairs instead of letters. The dots allow for more parametrical manipulations, and can help spread out test performance                                                                       |
| <b>Relational Encoding and Retrieval</b> | The Relational and Item Specific Encoding Task | A memory task, using object pictures, that controls the encoding strategies in order to minimize variance in memory retrieval due to uncontrolled individual differences in encoding the original material              |
| <b>Gain Control</b>                      | The Contrast-Contrast Effect Task              | Contrast sensitivity for a target is influenced by the contrast of the surround. Participants are asked to match a variable contrast patch to a central patch.                                                          |
| <b>Visual Integration</b>                | The Jitter Orientation Visual Integration Task | Examines changes in contour integration/perception by jittering the contour elements                                                                                                                                    |

# Talk Overview

## Three Parts

- What is Cognition?
- How do we measure cognitive functioning?
- How do we determine cognitive improvement?

# Relationships to Everyday Function

- To what extent does improvement on a clinical or lab based task indicate observable life gains?
- Functioning is multiply determined: Although scores on cognitive tests are associated with ratings of functioning, they account for only approximately one third of the variance in functioning of individuals with serious mental illness. (Depp, 2012; Bowie, 2010)
- There is currently no empirically based threshold to determine the degree of change in cognitive test performance that predicts meaningful changes in everyday functioning.

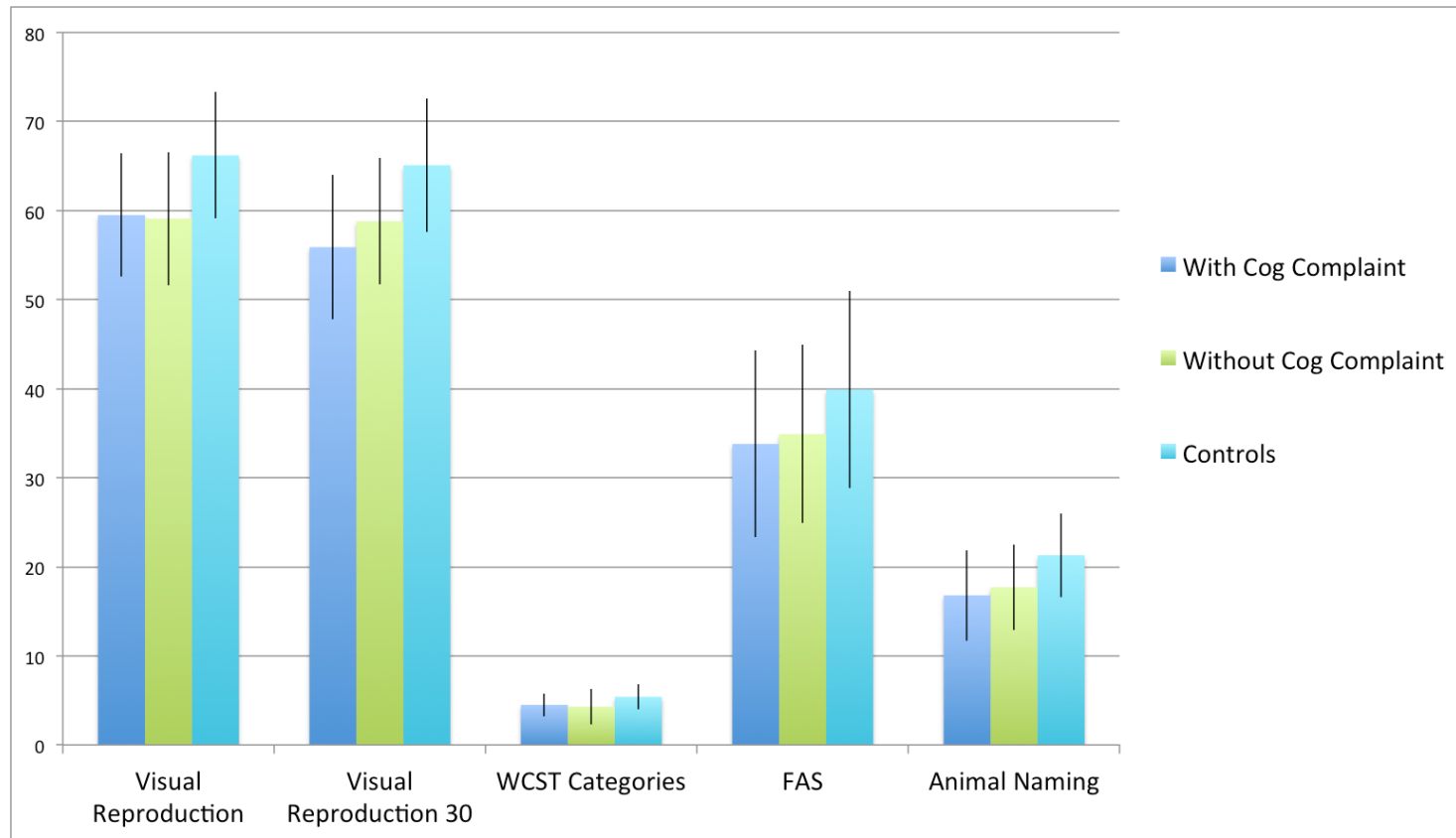


# Assessing Everyday Function

- Can we just ask the participant if their functioning has improved?
  - For individuals with bipolar and schizophrenia there is a strong inverse relationship between depression severity and self-ratings of functioning. (Harvey, 2015; Durand, 2015)
  - Treatment of mood symptoms may “improve” self-ratings of functioning, without any actual improvement of cognitive abilities.
- Some evidence that ratings of functioning made by high-contact clinicians, care-givers or family members are sometimes more accurate. (Sabbag, 2012)
- Novel methods of passive data collection – wearable devices and ecological momentary assessment – may help resolve the discrepancies between self report and actual functioning. (Shiffman, 2008)

# How well does self-report of cognition correlate with performance on cognitive tests?

**Patients with bipolar disorder with cognitive complaints do not perform worse than those without cognitive complaints.**



Adapted from Martinez-Aran et al., Psychother & Psychosom, 2005

# Subjective vs. Objective Measures

- Is a clinical objective measure more informative than self-report?
  - Self report can be dependent on mood state.
  - Is cognitive improvement detected by test performance but not noticeable to the patient an acceptable outcome?
  - The data are not conclusive regarding the extent to which improving someone's subjective sense of their cognitive abilities is related to improvement of functioning
  - In patients with schizophrenia, misestimation of ability was the strongest predictor of real-world functioning. Patients who were not able to accurately estimate their own ability were shown to have less real-world functioning abilities. (Gould, 2015; Naismith, 2007)

# How much impairment can we detect?

- Cognitive impairment in other mental disorders, such as schizophrenia, can be severe (approximately 1-2 SDs below healthy subjects).
- However, cognitive impairment in depression, while impactful to the patient, may be less obvious on some tests of cognition which are “too easy”
- Tests should be sensitive enough to detect slight changes in cognition, potentially with procedural modulations to make them harder and more sensitive

# Talk Overview

## Three Parts

- What is Cognition?
- How do we measure cognitive functioning?
- How do we determine cognitive improvement?
- How do we put this all together?

# Digit Symbol Substitution Test (DSST)

- The Digit Symbol Substitution Test has been widely used as a broadband, quick and sensitive measure of cognition in depression and other mental disorders as well
- DSST is thought to measure executive function, speed of processing and attention.

Digit symbol substitution test

|   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 |
| ↔ | ↑ | ≡ |   | ≠ | □ | Φ | ∈ | ≡ |

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|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 9 | 2 | 9 | 4 | 9 | 4 | 9 | 1 | 8 | 9 | 3 | 1 | 7 | 2 | 3 | 6 | 4 | 8 | 3 | 1 | 7 | 8 | 2 | 5 |
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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 4 | 7 | 1 | 7 | 5 | 8 | 4 | 1 | 5 | 2 | 6 | 9 | 9 | 5 | 6 | 7 | 6 | 2 | 9 | 4 | 8 | 7 | 2 | 8 | 6 |
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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 8 | 6 | 2 | 8 | 2 | 9 | 4 | 7 | 4 | 8 | 6 | 7 | 3 | 1 | 6 | 2 | 1 | 8 | 7 | 4 | 3 | 1 | 6 | 2 | 9 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 2 | 5 | 4 | 6 | 1 | 6 | 3 | 1 | 2 | 7 | 2 | 6 | 4 | 9 | 1 | 8 | 5 | 7 | 1 | 5 | 4 | 5 | 3 | 9 | 2 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 3 | 9 | 7 | 1 | 7 | 1 | 3 | 5 | 7 | 6 | 1 | 6 | 5 | 9 | 1 | 3 | 1 | 3 | 9 | 8 | 9 | 7 | 3 | 4 | 3 |
|   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

\*Part of the Weschler Adult Intelligence Scale, available from Pearson.

# Developing a Cognitive Battery for Depression

- DSST has been widely used and could be considered for inclusion as an implicit comparison to previous studies, but should not be a stand-alone measure for cognition
- Tests that measure other aspects of cognition affected by depression should be included
- Measures derived from cognitive neuroscience which assess more narrow aspects of cognition are preferable

# Conclusions

- There is probably no one test or set of tests that will be good for every study of cognition dysfunction in depression.
- However, appropriate measures should have:
  - Evidence of a valid behavioral/cognitive function
  - Evidence of impairment in depression
  - Evidence for an implementing neural system
  - Links to the mechanism of action of a pharmacological agent